PEG at 40°C *(Int. J. Pharm. (2001) 216(1-2) 9-16)*. Maejima *et al.* disclose the effect of a film coating made of talc and triethyl citrate on the stabilization of the release rate of theophyllin in a concentration of 20% from pellets coated with acrylic polymers *(Pharm. Dev. & Technol. (2001) 6(2) 211-21)*. Wesseling *et al.* disclose the effects of plasticization times, curing conditions, storage times and core properties on the release of an active substance and the reduction and thus a stable profile of the release of theophylline or chlorphenyramine maleate because of a thermal after-treatment, i.e. the curing of coated pellets *(Pharm. Dev. & Technol. (2001) 6(3) 325-31)*. Chen *et al.* disclose the effect of the composition and the structure of carriers on the release profile of diazepam from microspheres *(Shenyang Yaoke Daxue Xuebao (2001) 18(3), 162-5)*.

The patent application EP-A-454 396 discloses an improvement of tabletting properties if the active substance is pre-blended with citric acid, whereas JP patent application 60-163823 discloses e.g. tablets with clarithromycin and citric acid.

However, in the patent and other literature from this field no reference was found to be solving the present problem – i.e. to be dealing with or disclosing a pre-treatment or a humidification of an active substance at preparing a formulation, which would make possible or provide a stable and reproducible release profile of an active substance over the whole shelf life. Nor was found a reference dealing with the properties of an active substance extra requiring a stabilization of the release profile.

The Inventive Solution

One object of the invention is a method for a physical pre-treatment of an active substance, by which treatment technologically important physical properties of the active substance are so modified that a formulation prepared therefrom, useful for prevention and/or treatment in medicine, has a more stable release profile of the active

Example 1

Composition of a tablet:

Core	
micronized clarithromycin	500.0 mg
HPMC E50 Premium	200.0 mg
glyceryl behenate	250.0 mg
polyvinylpyrrolidone K-25	60.0 mg
microcrystalline cellulose	35.5 mg
stearic acid	15.0 mg
SiO_2 (aerosil 200)	5.0 mg
Ca stearate	25.0 mg
talc	5.0 mg
polyoxyethylene 20 oleate (polysorbate 80V)	24.5 mg
demineralized water	110.0 mg

Clarithromycin and a major part of PVP were pre-treated with an aqueous solution of PVP (minor part) and of polysorbate during stirring in a processor and then dried in a stream of hot air. The dry clarithromycin basis was homogenously blended with the excipients HPMC, glyceryl behenate, microcrystalline cellulose, Ca stearate, stearic acid, aerosil and talc. The mixture was tabletted.

Example 2

As Example 1 with the difference that a dry mixture of clarithromycin and of the whole amount of PVP was prepared and that it was humidified with water.

Example 3

Claims

1. A method for a physical pre-treatment of an active substance, wherein technologically important physical properties of the active substance are so modified as to enable the manufacture of a formulation having a more stable release profile of the active substance over the whole shelf life of the medicine than the profile would be with the same composition but without pre-treatment, characterized in that it comprises adding a poor solvent or a mixture of solvents to the active substance or to a mixture of the active substance with other excipients.

2. A method for a physical pre-treatment of an active substance according to claim 1, characterized in that said method comprises humidifying with water.

3. A method for a physical pre-treatment of an active substance according to claim 2, characterized in that the aqueous solution may contain various pharmaceutically acceptable excipients such as binders, buffers, emulgators, surfactants and others.

4. A method for a physical pre-treatment of an active substance according to claim 1, characterized in that the part of the active substance in the mass of the whole formulation is over about 30%.

5. A method for a physical pre-treatment of an active substance according to claim 1, characterized in that the part of the active substance in the mass of the whole formulation is over about 40%.

6. A method for a physical pre-treatment of an active substance according to claim 1, characterized in that the active substance is practically insoluble in the solvent used.

7. A method for a physical pre-treatment of an active substance according to claim 6, characterized in that the solvent used is water, wherein the solubility of the active substance is under about 0.1 g/L.

8. A method for a physical pre-treatment of an active substance according to claim 1, characterized in that the active substance, if micronized, is difficult to be directly tabletted or encapsulated.

9. A method for a physical pre-treatment of an active substance according to claim 1, characterized in that the particles thereof are large, brittle and/or porous.

10. A method for a physical pre-treatment of an active substance according to claims 1 to 9, characterized in that the active substance is clarithromycin.

11. A method for a physical pre-treatment of an active substance according to claim 10, characterized in that clarithromycin is micronized.

12. A method for a physical pre-treatment of an active substance according to claim 11, characterized in that the pre-treated, micronized clarithromycin enters a direct mixture for tabletting or encapsulating as a starting material.

13. A method for a physical pre-treatment of an active substance according to claims 1 to 12, characterized in that the obtained cores are coated.

14. A method for a physical pre-treatment of an active substance according to claim 13, characterized in that the coating also contains a polymer of a higher viscosity.

15. A method for a physical pre-treatment of an active substance according to claim 14, characterized in that the coating contains at least about 10% of a polymer of a higher viscosity.

16. A method for a physical pre-treatment of an active substance according to claims 14 to 15, characterized in that the polymer used in the coating has a viscosity of over about 6 mPas.

17. A film coating for a pharmaceutical formulation, which in the coating also contains a polymer of a viscosity of over about 6 mPas.

18. A pharmaceutical formulation with clarithromycin or analogues thereof, characterized in that the active substance is modified according to the method of claims 1 to 16.

19. A pharmaceutical formulation prepared according to the method of claims 1 to 16 for use in medicine for the treatment and prevention of diseases.

20. The use of a film coating composed of a combination of polymers having higher and lower molecular weights for coating tablet cores manufactured according to the method of claims 1 to 12.